REMARKS

Claims 10, 13 – 15, 39 – 50, and 72 – 76 are pending. The only remaining issues of patentability are written description and enablement. The claims have been amended to address the Examiner's concerns. Our comments regarding each ground of rejection follows.

I. Written Description

The rejection for lack of written description was maintained despite Applicants' amendment of the claims to require that the antisense nucleic acid be complementary to the 5' regulatory region of SEQ ID NO:3. The Examiner deemed the amendment and argument not to be persuasive for two reasons, stating:

> Firstly, claims 10, 13, 15, 39-42 are not limited to the eleven nucleotides that precede the initiation coding because the claims embody nucleotide sequence 10-50 nucleotides in length. Secondly, there is no disclosure of the sequence of the 5' regulatory region.

Applicants have now amended the relevant independent claims to require the specific sequence cggaccgtgca that corresponds to the 5' regulatory sequence of SEQ ID NO:3 and respectfully note that claim 10 requires an "antisense sequence consisting of 10 nucleotides in length". Claims 72 and 75 requires that the sequence be 10-20 or 10-50 nucleotides in length.

In response to the Examiner's first reason, amended claims 10, 72, and 74 are now limited to the eleven nucleotides cggaccgtgca that precede the initiation codon. Given that the sequence of the region in question is only 11 nucleotides in length

"cggaccgtgca", there are only two possibilities within the scope of the claim 10. Although claims 72 and 75 requires the antisense sequence to be 10-20 or 10-50 nucleotides in length, the sequence relative to SEQ ID NO:3 is unambiguously disclosed and the number of possibilities entirely manageable to the skilled artisan.

With regard to the Examiner's second reason that there is no disclosure of the sequence of the 5' regulatory region, Applicants repeat below passages of the specification that disclose the 5' regulatory region of SEQ ID NO:3 (page 4, lines 1-3, of the specification and page 7, lines 45-46, of the specification just below recitation of the nucleotide sequence of SEQ ID NO:3)

> Preferably, the antisense DNA is complementary to the 5' regulatory sequence or the 5' portion of the coding sequence of HAAH mRNA
>
> (SEQ ID NO:3 ; GENBANK Accession No. S83325; codon encoding initiating methionine is underlined).

Thus, the specification provides unambiguous disclosure of exactly what nucleotides of SEQ ID NO:3 represent the 5'regulatory region and what nucleotides represent the 5' portion of the coding sequence. In the latter case, the claims have been amended to require that the 5' portion of the coding sequence includes the codon initiating methionine.

Independent claim 43 requires that the antisense sequence be complementary to sequences of SEQ ID NO:3 that include the ATG initiating methionine codon and that the antisense sequence is 10-50 nucleotides in length. Again, the actual sequence required by the claims is unambiguously described in the specification and by the recitation of the nucleotides of SEQ ID NO:3.

To satisfy the written description requirement, an Applicant must convey with reasonable clarity to those skilled in the art as of the filing date that he or she was in

possession of the invention as claimed, i.e., does the disclosure reasonably convey to the artisan that the inventor has possession of the invention as claimed (MPEP at 2163.02). In view of these amendments and clarifications as supported by literal disclosure in the originally-filed specification, Applicants submit that the standard for complying with the written description requirement has been met.

II. Enablement

The rejection for lack of enablement was also maintained.

In a previous submission, Applicants presented to the Patent Office evidence that three different antisense oligonucleotides that fall within the scope of the amended claims inhibited tumor growth. The Examiner stated:

> This has been considered but not found persuasive. The instant claims are directed to the anti-sense modulation of the human AAH, and read on the inhibition of tumor growth in a human patient by the administration of a nucleic acid vector which transcribes a polynucleotide which is complementary of the HAAH regulatory coding sequence which is not disclosed. In the event that the claims were drawn to encompass a complementary coding region with in SEQ ID NO:3, the specification is not enabling for the claims requiring the inhibition of tumor growth in a mammal, which reads on the treatment of a human patient with a naturally-occurring tumor for the following reasons.

The reasons that were given by the Examiner have largely to do with dosage and administration as evidenced by citations to ISIS antisense drugs that did not show clinical efficacy. To summarize, the Examiner stated:

> These reference[s] serve to demonstrate that there is no absolute nexus between the inhibition of tumor cells by administration of anti-sense oligonucleotide in a tumor model or in vitro, with the administration of anti-sense oligonucleotides to a patient with a tumor.

This statement seems to indicate that the Examiner is not willing to acknowledge anything short of human clinical trial data to fulfill the enablement requirement. This position is inconsistent with the statutory requirements.

In the present case, Applicants have defined the target gene and indeed the specific target sites within the gene (and amended the claims to recite the sequence) and have shown efficacy in an art-recognized model for human cancer. Methods of administering and dosing antisense compositions are described on pages 17-20 of the specification. This information taken in context with the general knowledge and expertise of the skilled artisan more than fulfills the requirements for enablement. Exact dosages that would be applicable in all situations are not described per se, because as is well known in the art, such amounts and dosage schedules are routinely adjusted by the clinician to suit a particular patient or circumstance. Therefore, this ground for rejection should also be withdrawn.

CONCLUSION

Applicants respectfully submit that claims 10, 13 – 15, 39 – 50, and 72 – 76 are now in condition for allowance. The Examiner is invited to contact the undersigned at the number or email listed below should she believe there are any remaining issues that could be more easily resolved by personal or telephonic interview.

The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21486-032.

Respectfully submitted,

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